REMARKS

This is meant to be a complete response to the Office Action mailed October 31, 2007. In the Office Action, the Examiner rejected claims 31-37, 42, 45-51, 60 and 61 under 35 U.S.C. 112, first paragraph (written description requirement); claim 34 under 35 U.S.C. 112, first paragraph (written description requirement); claim 34 under 35 U.S.C. 112, first paragraph (enablement requirement); and claims 50 and 51 under 35 U.S.C. 112, second paragraph. In addition, the Examiner also rejected claims 31-37, 42, 45-51, 60 and 61 under 35 U.S.C. 103(a) as being unpatentable over US 5,482,841 in view of US 5,292,641; Prilliman et al.; DiBrino et al.; and US 6,232,445.

Applicants' Response to the 35 U.S.C. 112, ¶1 and ¶2 Rejections

In the Office Action, the Examiner rejected claims 31-37, 42, 45-51, 60 and 61 under 35 U.S.C. 112, first paragraph (written description requirement); claim 34 under 35 U.S.C. 112, first paragraph (written description requirement); claim 34 under 35 U.S.C. 112, first paragraph (enablement requirement); and claims 50 and 51 under 35 U.S.C. 112, second paragraph.

In response to the rejection of claims 31-37, 42, 45-51, 60 and 61, the claims have been amended herein to recite that each trimolecular complex of the pool of functionally active, recombinantly

produced, truncated individual soluble MHC trimolecular complexes has the same recombinant, soluble MHC heavy chain allele.

In response to the rejections of claim 34, such claim has been amended to delete the terms "and combinations thereof" from the claim.

In response to the rejection of claims 50 and 51, claim 50 has been amended herein.

Therefore, Applicants respectfully submit that the claims as currently pending fully comply with all of the requirements of 35 U.S.C. 112. Thus, Applicants respectfully request that each of the 35 U.S.C. 112, ¶1 and ¶2 rejections be reconsidered and withdrawn.

Applicants' Response to the 35 U.S.C. 103(a) Rejection

In addition, the Examiner also rejected claims 31-37, 42, 45-51, 60 and 61 under 35 U.S.C. 103(a) as being unpatentable over US 5,482,841 in view of US 5,292,641; Prilliman et al.; DiBrino et al.; and US 6,232,445. Applicants respectfully traverse the rejection based on the amendments to the claims and for the reasons stated herein below.

The present invention, as recited in the amended claims, is a method for detecting the presence of anti-MHC antibodies in a sample. In the method a pool of functionally active, recombinantly produced,

truncated individual soluble MHC trimolecular complexes is obtained by the steps of isolating mRNA encoding at least one MHC heavy chain allele from a source, reverse transcribing the mRNA to obtain cDNA; identifying an individual MHC heavy chain allele in the cDNA; and PCR amplifying the individual MHC heavy chain allele in a locus-specific manner to produce a PCR product having the coding regions encoding cytoplasmic and transmembrane domains of the individual MHC heavy chain allele removed such that the PCR product encodes a truncated, soluble form of the individual MHC heavy chain molecule. The PCR product is then cloned into a mammalian expression vector, thereby forming a construct that encodes the individual soluble MHC heavy chain molecule, and the construct is transfected into a **mammalian cell line that expresses endogenous MHC molecules**. The mammalian cell line is then cultured under conditions which allow for expression of the recombinant individual soluble MHC heavy chain molecule from the construct, such conditions also allowing for endogenous loading of a peptide ligand into the antigen binding groove of each individual soluble MHC heavy chain molecule in the presence of beta-2-microglobulin to form the individual soluble MHC trimolecular complexes prior to secretion of the individual soluble MHC trimolecular complexes from the cell, wherein each trimolecular complex comprises a recombinant, soluble MHC heavy chain allele, beta-2-microglobulin

and endogenously loaded peptide and wherein each trimolecular complex of the pool of functionally active, recombinantly produced, truncated individual soluble MHC trimolecular complexes has the same recombinant, soluble MHC heavy chain allele. The individual, soluble MHC trimolecular complexes are then purified substantially away from other proteins and maintain the physical, functional and antigenic integrity of the native MHC trimolecular complex.

At least one soluble MHC trimolecular complex is then linked directly or indirectly to a substrate such that it retains the physical, functional and antigenic integrity of the native MHC trimolecular complex. A sample is then reacted with the substrate/MHC trimolecular complex and washed to remove unbound portions of the sample; the substrate/MHC trimolecular complex is then reacted with means for detecting anti-MHC antibodies, and it is determined that anti-MHC antibodies specific for the individual MHC molecule are present in the sample if the means for detecting anti-MHC antibodies is positive.

The fact that the Examiner had to combine teachings from five different references in the 35 U.S.C. 103(a) rejection demonstrates that a case of *prima facie* obviousness has not been established, and that the Examiner has impermissibly used "hindsight", based on the teachings provided in the subject application, to hunt through the prior

art for the claimed elements and combine them as claimed, and such approach is "an illogical and inappropriate process by which to determine patentability" (*Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570, 38 USPQ2d 1551, 1554 (Fed. Cir. 1996). However, Applicants respectfully submit that the presently claimed invention is not obvious over the teachings of all five references, as described in more detail herein below.

US 5,482,841 teaches a method of evaluating transplant acceptance using **membrane bound alloantigen that has been extracted from cells with a mild detergent** (see Column 2, lines 14-16; Column 3, lines 32-49). The alloantigen is indirectly attached to a solid support, contacted with a biological sample, and washed; the presence of bound alloantigen-specific receptor is then detected with a labeled reagent. The '841 patent does not teach, disclose or even suggest a method that utilizes soluble MHC trimolecular complexes, and most certainly does not teach that same soluble MHC trimolecular complexes are produced in a mammalian cell line that expresses endogenous MHC molecules.

The Examiner has recognized the deficiencies of the '841 patent, and has attempted to supply the same with **FOUR** secondary references.

The '641 patent adds nothing to supply the defect of the '841 patent; that is, the '641 patent also does not teach, disclose or even suggest a method that utilizes soluble MHC trimolecular complexes, and most certainly does not teach that same soluble MHC trimolecular complexes are produced in a mammalian cell line that expresses endogenous MHC molecules.

While it is agreed that Prilliman et al. teaches production of soluble HLA molecules, Prilliman et al. specifically teach the use of a Class-I deficient HLA cell line (see Page 380, Column 2, lines 22-25). Therefore, Applicants respectfully submit that Prilliman et al. does not teach, disclose or even suggest producing soluble MHC trimolecular complexes in a mammalian cell line that expresses endogenous MHC molecules. Moreover, a person having ordinary skill in the art would be aware that **all MHC/HLA purification methods prior to the present invention utilized MHC/HLA-deficient cell lines**, so that endogenously produced MHC/HLA did not interfere with the purification methods. In fact, prior to the present invention, it was very difficult if not impossible to separate recombinantly produced MHC from endogenously produced MHC when both were produced by a single cell. Therefore, the presently claimed invention is nonobvious over the prior art in that it produces soluble HLA molecules in ANY cell line, and does not require that the cell line be HLA-deficient.

DiBrino et al. teaches production of full-length HLA in a Class I-deficient HLA cell line, and therefore does not supply the deficiencies of the other prior art references.

The '445 patent teaches production of an MHC-peptide fusion protein, wherein the MHC molecular complex is produced as a single chain and the peptide is fused into the peptide binding groove of the MHC molecule. Therefore, the '445 patent actually teaches away from the claim limitations of allowing for endogenous loading of a peptide ligand into the antigen binding groove of each individual soluble MHC heavy chain molecule in the presence of beta-2-microglobulin to form the individual soluble MHC trimolecular complexes prior to secretion of the individual soluble MHC trimolecular complexes from the cell, wherein each trimolecular complex comprises a recombinant, soluble MHC heavy chain allele, beta-2-microglobulin and endogenously loaded peptide. Thus, the '445 patent does nothing to supply the deficiencies of the other prior art references cited by the Examiner, and further, cannot be combined with any other references to render the presently claimed invention obvious.

Therefore, Applicants respectfully submit that amended claims 31-37, 42, 45-46, 48-51 and 60-61 are non-obvious over the combination of references set forth above. Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. 103(a)

rejection of currently pending claims 31-37, 42, 45-46, 48-51 and 60-61 over US 5,482,841 in view of US 5,292,641; Prilliman et al.; DiBrino et al.; and US 6,232,445.

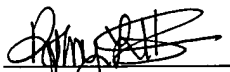
CONCLUSION

This is meant to be a complete response to the Office Action mailed October 31, 2007. Applicants respectfully submit that each and every rejection of the claims has been overcome. Further, Applicants respectfully submit that pending claims 31-37, 42, 45-46, 48-51 and 60-61, as now amended, are free of the prior art of record and are in a condition for allowance. Favorable action is respectfully solicited.

In addition, claims 38-41 are currently withdrawn; however, upon allowance of any of claims 31-37, 42, 45-46, 48-51 and 60-61, Applicants respectfully request rejoinder and reconsideration of currently withdrawn claims 38-41. In addition, the Examiner previously required election of a single disclosed species to be used in the claimed method (i.e., a specific substrate, soluble HLA molecule, antibody and anchoring moiety). Upon allowance of any of claims 31-37, 42, 45-46, 48-51 and 60-61, Applicants respectfully request rejoinder and reconsideration of all disclosed and claimed species (i.e., all specific substrates, soluble HLA molecules, antibodies and anchoring moieties).

Should the Examiner have any questions regarding this amendment, or the remarks contained therein, Applicants' representative would welcome the opportunity to discuss the same with the Examiner.

Respectfully submitted,



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